VALOCTOCOGENE ROXAPARVOVEC GENE TRANSFER IN PARTICIPANTS WITH HIV

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DISCLOSURE FOR **MARGARET V RAGNI**

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Shareholder	No relevant conflicts of interest to declare
Grant / Research Support	Alnylam/Sanofi, BioMarin Pharmaceutical Inc., Bioverativ/Sanofi, Spark Therapeutics, Takeda Pharmaceuticals USA
Consultant	Alnylam/Sanofi, BioMarin Pharmaceutical Inc., Bioverativ/Sanofi, Spark Therapeutics, and Takeda Pharmaceuticals USA
Employee	No relevant conflicts of interest to declare
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Speaker bureau	No relevant conflicts of interest to declare
Other	Takeda Pharmaceuticals USA (receipt of study drug for investigator-initiated trials)

Presentation includes discussion of the following off-label use of a drug or medical device:
<N/A>

INTRODUCTION AND OBJECTIVES

- Valoctocogene roxaparvovec transfers a B-domain deleted human FVIII coding sequence controlled by a hepatocyte-selective promoter using an AAV5 vector, enabling endogenous FVIII production[1–4]
  - In a phase 3 trial, 132 men with severe haemophilia A and who were negative for HIV had significantly increased FVIII production and bleeding reduction through 52 weeks post-valoctocogene roxaparvovec gene transfer[4]
  - Participants with HIV were initially eligible, but were excluded by protocol amendment due to potential liver toxicity with concomitant HIV antiviral agents
- Transfusion-associated HIV infection is common in individuals with haemophilia A, and efficacy and safety of AAV-mediated gene transfer in people with HIV is unknown
- Here, we present safety and efficacy results from 3 men with HIV and haemophilia A who received valoctocogene roxaparvovec gene transfer in two phase 3 trials, specifically 301 (NCT03370913) and 302 (NCT03392974)

METHODS

- In both trials, eligible participants were men who were ≥18 years with severe haemophilia A (FVIII ≤1 IU/dL) previously receiving prophylactic exogenous FVIII and negative for inhibitors and anti-AAV5 antibodies
- Participants received a single infusion of valoctocogene roxaparvovec:
  - Participants in 301 received a $6x10^{13}$ vg/kg dose
  - The participant in 302 received a $4x10^{13}$ vg/kg dose
- Efficacy was assessed by a change from baseline in FVIII activity and annualised treated bleeding and exogenous FVIII usage after week 4, the scheduled end of regular FVIII prophylaxis
- Safety was assessed by AE type and frequency and clinical laboratory tests
- An in vitro hepatocyte model was used to investigate potential drug-drug interactions

RESULTS

Participant demographics and baseline characteristics

- Overall, 3 participants with HIV enrolled in 301 or 302

	Participant 1	Participant 2	Participant 3
Age at enrolment, years	52	49	45
History of hepatitis B exposure	Y	Y	N
History of hepatitis C exposure	Y	Y	Y
Number of problem joints	0	0	6
Baseline annualised FVIII use			
Infusions/year	80.0	118.8	101.7
IU/kg/year	3271.2	5249.1	5487.2
Baseline ABR (treated bleeds), bleeds/year	2.8	5.8	12.7
Baseline HAART regimen	Eviplera, dolutegravir	Darunavir, dolutegravir, ritonavir	Efavirenz, lamivudine, tenofovir disoproxil fumarate
Valoctocogene roxaparvovec dose, vg/kg	$6x10^{13}$	$6x10^{13}$	$4x10^{13}$
Follow-up at data cutoff date, weeks	115	124	106

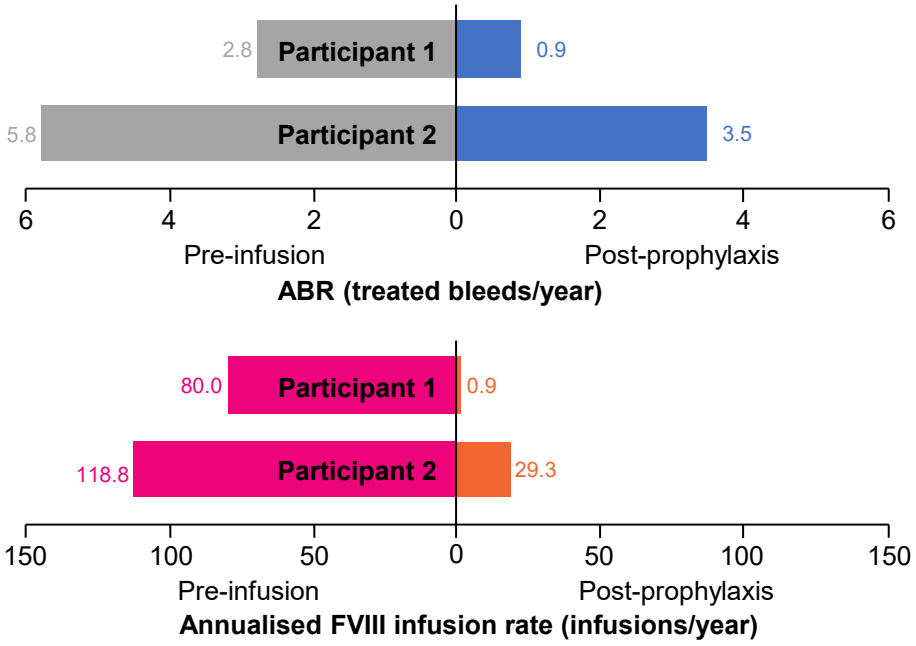
AAV, adeno-associated virus; AAV5, AAV serotype 5; ABR, annualised bleeding rate; AE, adverse event; FVIII, factor VIII; HAART, highly active anti-retroviral therapy; HIV, human immunodeficiency virus.

1. Rangarajan S, et al. *NEJM.* 2017;377:2519–30. 2. Pasi KJ, et al. *NEJM.* 2020;382:29–40. 3. Pasi KJ, et al. *Haemophilia.* 2020;26:151. 4. Ozelo MC, et al. *RPTH.* 2021;5(suppl 1).

EFFICACY

- At week 52 post-gene therapy, Participants 1 and 2 had FVIII per CSA of 24.3 and 6.1 IU/dL, respectively
  - Both had reduced bleeding and FVIII utilization compared to baseline (Figure 1)
- At week 3, Participant 3 had FVIII activity of 11.5 IU/dL per CSA; between weeks 5 and 46, his FVIII ranged from <3 to 9.7 IU/dL
  - He had 16 treated bleeds during this period, and resumed routine FVIII prophylaxis on week 49

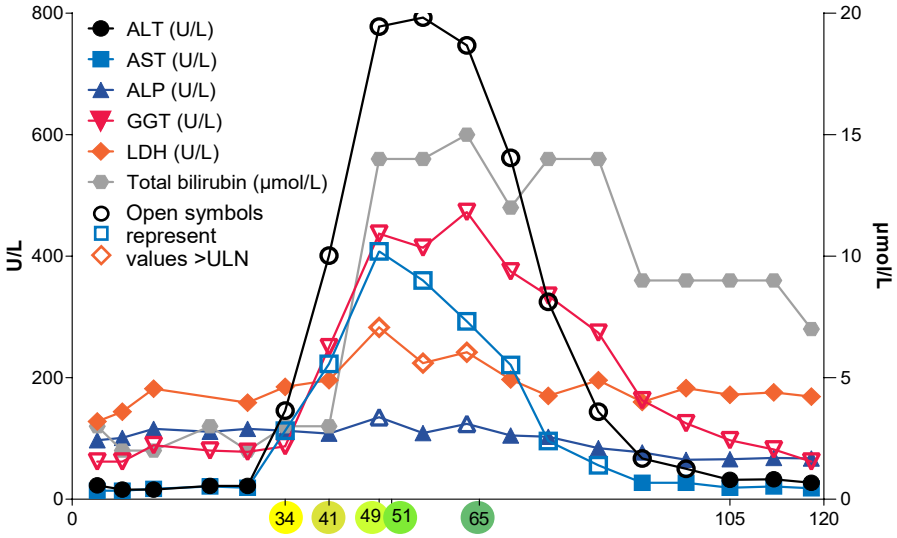
Figure 1. Participant 1 and 2 bleeding and FVIII use after week 4



SAFETY

- Participant 1 experienced 6 AEs of Grade ≤2; none were liver enzyme elevations
- Participant 2 experienced 50 Grade 1 AEs and 2 SAEs (upper respiratory infection; traumatic haematoma). AEs of Grade 1 elevated AST were reported on days 85 and 107. Prednisolone 60 mg/d was initiated on day 109, and AEs resolved
- Participant 3 reported 15 AEs, including Grade 3 SAEs of ALT increase and hepatocellular injury beginning on day 41 and resolving on day 105 (Figure 2)
  - He remained asymptomatic throughout, and extensive hepatic workups revealed no alternative etiologies

Figure 2. Liver function test results for Participant 3



Day 34
- Grade 2 ALT and AST elevation
- Prednisolone 60 mg/d initiated

Day 41
- Grade 3 ALT elevation
- Grade 3 hepatocellular injury

Day 49
- Peak AST (408 U/L)
- Peak GGT (437 U/L)

Day 51
- Peak ALT (807 U/L)

Day 65
- Efavirenz-containing HAART stopped
- Replaced with raltegravir and emitricitabine/ tenofovir alafenamide

ABR, annualised bleeding rate; AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CSA, chromogenic substrate assay; FVIII; factor VIII; GGT, gamma-glutamyl transferase; HAART, highly active anti-retroviral therapy; HIV, human immunodeficiency virus; LDH, lactate dehydrogenase; SAE, serious AE; ULN, upper limit of normal.

IN VITRO DRUG-DRUG INTERACTION ANALYSIS

- ALT elevations for Participant 3 likely resulted from drug interactions between the efavirenz component of his HAART regimen and valoctocogene roxaparvovec
- An in vitro model of primary hepatocytes was used to further investigate this hypothesis
  - Hepatocytes were incubated with efavirenz and valoctocogene roxaparvovec, and cell death and transgene DNA and RNA were assessed; measurements were also taken 72 hours after efavirenz withdrawal
- Efavirenz was cytotoxic at doses 5x and 20x C_{max}, the estimated steady-state peak plasma level of the human dose; effects did not synergise with valoctocogene roxaparvovec (Figure 3)
- For hepatocytes incubated with valoctocogene roxaparvovec, efavirenz significantly decreased transgene RNA and RNA/DNA levels (Figure 4)

Figure 3. Efavirenz cytotoxicity

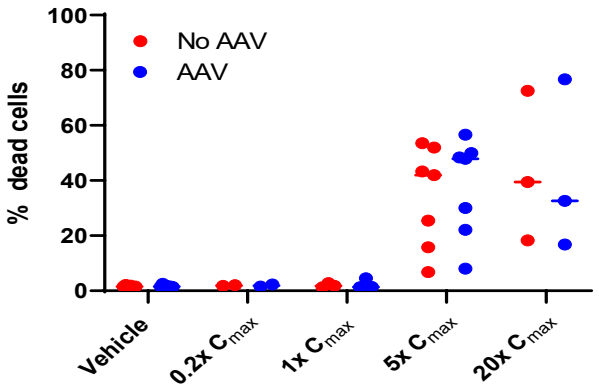
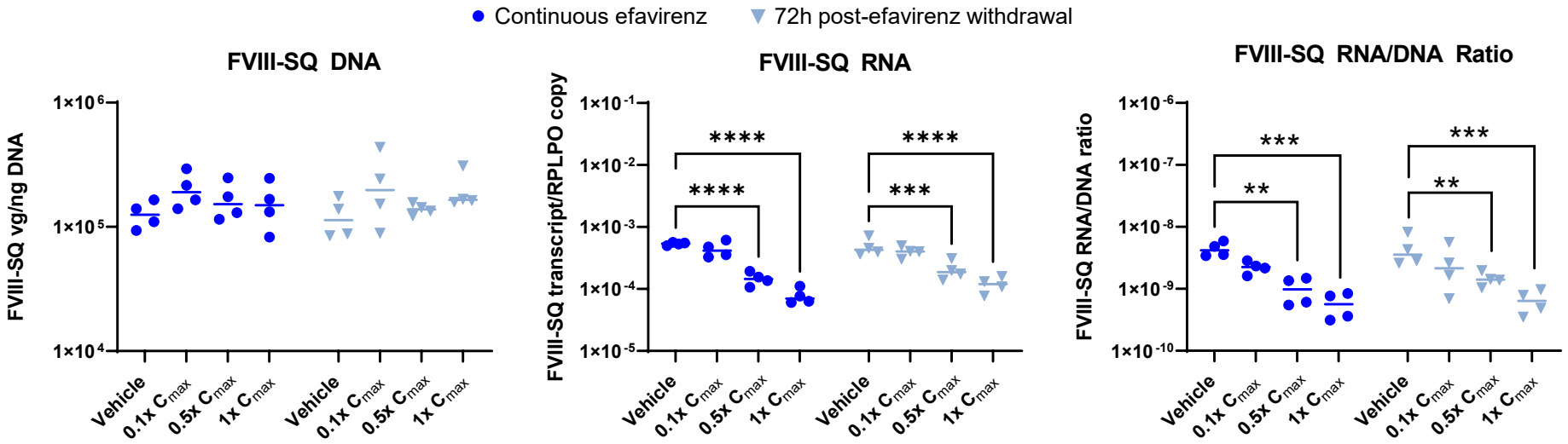


Figure 4. Transgene DNA and RNA with continuous efavirenz and 72 hours post-withdrawal



**P <0.05; **P <0.01; ***P <0.001; ****P <0.0001*

CONCLUSIONS

- After valoctocogene roxaparvovec gene transfer, 2 participants with HIV had increased FVIII expression and reduced bleeding. These participants had no or only Grade 1 liver function test AEs
- One participant with HIV had hepatic enzyme elevation unresponsive to corticosteroids, likely due to an interaction between gene therapy and efavirenz, a known hepatotoxic agent. This participant did not have sustained FVIII production post-gene therapy and, thus, resumed prophylaxis
- In vitro experiments with efavirenz confirmed its hepatoxicity and suggest it may inhibit FVIII-SQ transgene RNA production

AAV, adeno-associated virus; AE, adverse event; ALT, alanine aminotransferase; C_{max}, maximum concentration; FVIII-SQ, factor VIII SQ variant; h, hour; HAART, highly active anti-retroviral therapy; HIV, human immunodeficiency virus; hr, hour; RPLPO, Large Ribosomal Protein.